I. Remarks

Claims 1-52 are currently pending.

Applicants thank the Office for indicating that claims 5-16, 23-34, and 38-49 represent allowable subject matter.

Applicants further thank the Office for pointing out that no concise explanation of the relevance of citation no. 21 (EP 0 775 750) was provided with the information disclosure statement filed on March 31, 2005. Pursuant to 37 C.F.R. § 1.98(a)(3), Applicants hereby sets forth the explanation of the reference. Applicants believe that EP 0 775 750 relates to fusion proteins derived from furin or furin analogs and to methods to prepare proteins from proproteins by using the fusion protein. This patent is relevant as background to the instant invention as it discusses furin and furin cleavage sites, which are used in the instant invention to create engineered FVII. Applicants have also provided with this communication a copy of the U.S. Patent No. 6,210,929 that claims priority to EP 0 775 750. Therefore, Applicants respectfully request that EP 0 775 750 be considered by the Examiner. Once the Examiner has considered the reference, Applicants further request that the IDS submitted herein be initialed and returned.

II. Claim rejections under 35 U.S.C. § 112

Claims 2, 4, 17-18, 20, 22, 35, 37, 50, and 52 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in such a way as to enable the skilled artisan to make and/or use the instant invention. In particular, the Office has concluded that it would have required undue experimentation to practice the instantly claimed invention because the SKI-1 consensus sequence as taught in the art at the time of the invention and SEQ ID NO. 9 are not the same.

Applicants respectfully traverse. The instant application does not define SEQ ID NO. 9 as a consensus site for SKI-1but merely offers it as a potential recognition site for SKI-1 cleavage in an engineered FVII molecule. In contrast to the Office's assertion of non-enablement, the instant application provides sufficient guidance as to sequences capable of cleavage by SKI-1 for an artisan to practice the invention as claimed. The SKI-1 cleavage site consensus sequences were known in the art at the time of filing, several cleavage site sequences are incorporated by reference into the instant specification, and SEQ ID NO. 9 provides an example of such a potential sequence.

A patent does not need to teach, and preferably omits that which is well-known in the art (MPEP 2164.01). Therefore, Applicants assert that the absence of published consensus sequence for SKI-1 in

the instant specification is not fatal. The artisan of ordinary skill, in October 2001, could have identified the SKI-1 consensus sequences (published two years prior in 1999) and routinely used them in the practice of the instant invention.

The instant specification provides several SKI-1 cleavage site sequences through incorporation of the Seidah et al. reference on page 26, lines 15-19 of the instant specification. This reference provides guidance to the artisan as to possible sites for use in designing an appropriate cleavage site within the FVII molecule. In addition, the SKI-1 cleavage site consensus sequences were known in the art at the time the instant specification was filed. This is demonstrated by the reference Seidah et al. (1999) Brain Research, Vol. 848, 45-62, which was cited by Office in the instant rejection.

Furthermore, Applicants respectfully disagree with the Office's conclusion that the instant specification teaches that the SKI-1 consensus sequence is SEQ ID NO. 9. The specification does teaches that the SKI-1 cleavage site is an alternate site to a furin cleavage site for use in the FVII constructs of the instant invention (see page 26, line 15.) It directs the artisan to the Seidah et al. (1999) PNAS reference by incorporation (see page 26, lines 15-19.) It then provides that FVII may be modified to create a recognition site for SKI-1 and cites Figure 3 as one example of such a site. Neither the specification nor Figure 3 teaches that SEQ ID NO. 9 is the SKI-1 consensus site. Rather, SEQ ID NO. 9 is an example of a potential SKI-1 cleavage site for use in the instant invention.

The fact that SEQ ID NO. 9 does not precisely correspond to the published consensus sequences is not fatal to the enablement issue. A consensus sequence by nature does not define with absolute specificity the entire group of cleavage sites for a particular protease. Rather, it is a theoretical construct that comprises the amino acids that appear most frequently at each position when an artisan compares a series of sequences that are actually cleaved by the protease. For example, such a lack of precise correspondence is demonstrated by the Seidah et al. (1999) Brain Research reference itself (see section 4 on page 57.) Therefore, with respect to SEQ ID NO. 9, the skilled artisan could use SEQ ID NO. 9 to construct a FVII construct. The skilled artisan would have no reason to doubt the teachings of the instant specification, nor has the Office provided an objective reason for such a doubt.

Applicants assert that the skilled artisan would have been able to practice the instant invention without undue experimentation. The instant specification provides enabling guidance to practice the instant invention by identifying the SKI-1 cleavage site as useful. The SKI-1 consensus sequence was published at the time the instant specification was filed as shown by the Seidah et al. Brain Research reference cited by the Office. The instant specification also directs the artisan to a more complete description of the SKI-1 proprotein convertase by reference, and identifies a specific, potential cleavage

site as SEQ ID NO. 9. Therefore, the skilled artisan would have been able to build the FVII constructs with SKI-1 cleavage sites with only routine experimentation using the instant specification as a guide. The artisan would be able to test for SKI-1 cleavage using the assays specifically described in the art at the time the application was filed. The artisan would also be able to practice routine experimentation, using the assays provided by the instant specification, to determine if the engineered FVII was active when cleaved by SKI-1. Applicants note that a significant amount of experimentation is permitted in order to practice an invention so long as it is routine. Applicants assert that this represents such routine experimentation. Accordingly, withdrawal of this rejection is respectfully requested.

III. Claim rejections under 35 U.S.C. § 102(e)

Claims 1, 3, 18-19, 21, 36, and 51 stand rejected as allegedly being anticipated by WO 01/70763 (High et al., 2001), which designated the U.S. and was published in English and claims priority to U.S. Provisional application no. 60/191,331 filed on March 22, 2000. Specifically, the Office has concluded that WO 01/70763 teaches both the insertion of a furin cleavage site or the substitution of a furin cleavage sequence for the native cleavage site. Applicants respectfully traverse this rejection because the Office has impermissibly relied on disclosure in WO 01/70763, which was not present in the provisional application no. 60/191,331 filed on March 22, 2000.

In setting forth the instant rejection, the Office cites a passage from WO 01/70763 on page 15, lines 13-16, which teaches an embodiment of the invention wherein an engineered cleavage site will substitute for the native cleavage site. The Office concludes that this teaching reads upon the instant claims. Applicants respectfully assert that this passage, whether or not it reads upon the instant claims, is not proper prior art to said claims.

WO 01/70763 claims priority to the 60/191,331 application, filed March 22, 2000, and was filed as a PCT application on March 22, 2001. The instant application claims similarly claims priority to a provisional patent application, 60/243,046, filed on October 25, 2000[1]. Therefore, Applicants respectfully assert that only the subject matter present in the 60/191,331 application, filed March 22, 2000, can properly be considered prior art against the instant claims since the filing date of the instantly claimed subject matter is October 25, 2000.

The passage cited by the Office as anticipatory from WO 01/70763 on page 15, lines 13-16 was not present in the 60/191,331 application. The only disclosure present in the 60/191,331 application,

[1] The instant application also claims priority to a second provisional application, 60/307,492, filed on July 24, 2001. However, the subject matter relevant to the instant issue was present in the first provisional to which priority was claimed. Therefore, the second provisional is not discussed in order to avoid redundancy.

which relates to protease cleavage sites for use in an engineered FVII, is located on page 2, in the first full paragraph reproduced below.

> "The invention proposes the use of an engineered factor VII such that upon synthesis and secretion from the cell, it is released as active factor VII such that upon synthesis and secretion from the cell, it is released as active factor VII (FVIIa). In order to accomplish this a protease cleavage site (such as, but not limited to, a PACE/furin site) will be inserted at the normal site of activation (between amino acids Arg^{152} - Ile^{153}). Thus, upon synthesis of the engineered factor VII in the endoplasmic reticulum and Golgi apparatus, the protease recognizing the inserted cleavage site will proteolyze the engineered factor VII releasing a small peptide and generating two chain activated factor VII (FVIIa) which is then released into circulation."

The language of this passage unequivocally states that "...a protease cleavage site (such as, but not limited to, a PACE/furin site) will be inserted at the normal site of activation (between amino acids Arg^{152} - Ile^{153})." Furthermore, the passage contemplates that a small peptide and two chains will be released upon cleavage of the construct. It does not give alternative means to accomplish the generation of an engineered factor VII nor would the skilled artisan read the passage to suggest that alternates are part of the invention.

Figure 1 of the 60/191,331 application provides the same disclosure. This flow diagram shows that the cleavage site is inserted into the FVII molecule to produce an engineered FVII. Intracellular processing of the construct leads to generation of activated FVII and removal of the protease cleavage site. Again, Figure 1 does not teach or suggest the embodiment cited by the Office anticipatory from WO 01/70763.

As argued earlier in the prosecution of this case, the disclosure of the 60/191,331 application does not and cannot anticipate the instant claims. In the particular embodiment claimed herein, Applicants utilize modified Factor VII polypeptides capable of conversion to activated Factor VII when expressed in an individual. The endogenous Factor VII activation cleavage sequence is mutated to encode for a non-endogenous enzymatic cleavage site capable of being cleaved when expressed intracellularly (see the instant specification at page 6, lines 27-29.) Intracellular cleavage of this polypeptide results in the generation of only a Factor VII heavy chain and a Factor VII light chain.

In contrast, the 60/191,331 teaches the <u>insertion</u> of additional amino acid sequences that code for an enzymatic cleavage site into the human Factor VII sequence rather than mutation of the endogenous sequence. By utilizing insertion rather than mutation, intracellular cleavage of the 60/191,331 polypeptide results in the generation of a small peptide comprising some portion of the inserted sequence, a Factor VII heavy chain, and a Factor VII light chain. Therefore, the 60/191,331 application cannot anticipate the instant claims because the methods taught therein utilize different DNA vectors from those of the instant claims and the polypeptides produced by the 60/191,331 methods are

different from those of the instant claims as well. Accordingly, Applicants respectfully request that this rejection be withdrawn.

IV. Claim rejections under 35 U.S.C. § 103(a)

Claims 2, 4, 20, 22, and 37 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 01/70763 (High et al., 2001), in view of Seidah et al. (1999) Brain Research, vol. 848, 45-62. In particular, the Office has concluded that it would have been obvious to one of ordinary skill in the art to substitute the SKI-1 cleavage site provided by Seidah et al. for the furin site in the High et al. vectors, in light of the motivation provided by High et al. to modify FVII. Applicants respectfully traverse because the disclosure utilized by the Office in setting forth the instant rejection is not proper prior art to the instant claims.

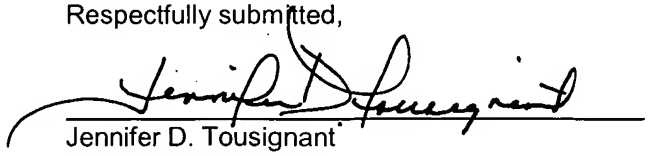
As discussed supra, only the subject matter present in the 60/191,331 application, filed March 22, 2000, can properly be considered prior art against the instant claims. The passage cited by the Office from WO 01/70763 as providing motivation to combine WO 01/70763 with Seidah et al. was not present in the 60/191,331 application. Absent a motivation to combine, and absent a teaching of mutation rather than insertion, a prima facie case of obviousness cannot and has not been established. As such, Applicants respectfully request withdrawal of the instant rejection.

V. Conclusion

No fee is deemed necessary in connection with the filing of this communication. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 07-1074.

Respectfully submitted,

12/28/05
Date



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